REMARKS

Entry of the foregoing, and further and favorable reconsideration of the subject application, are respectfully requested.

Applicants gratefully acknowledge the courtesy shown by the Examiner to their undersigned representative in the personal interview held September 5, 2002.

By the present amendment, claims 39, 41, 45, 49, 55 and 57 have been canceled without prejudice or disclaimer to the subject-matter claimed therein. Independent claims 1, 2, and 22 have been amended to incorporate the subject-matter of dependent claims 39 or 41. Support for these amendments can also be found in the specification at least on page 20 last paragraph to page 21, first paragraph and page 42 (Example 6). The independent claims have also been amended to delete the proviso that the "sense and antisense sequence are not naturally occurring simultaneously in one RNA molecule." No new matter has been added by these amendments.

Claim Rejections - 35 U.S.C. § 112

Turning now to the Official Action, Claims 1,4, 8, 40 and 41 have been rejected under 35 U.S.C. §112, second paragraph, as purportedly indefinite. This rejection, to the extent that it applies to the claims as amended, is respectfully traversed.

At page 2 of the Official Action, the Examiner asserts that Claim 1 is indefinite due to the recitation of "the annealing RNA sequences" in line 7 of the claim, arguing that there is insufficient antecedent basis for this limitation in the claim. Without conceding to the merits of this rejection, by the present amendment Applicants have amended claim 1 to recite that the artificial hairpin comprises two annealing RNA sequences.

At page 3 of the Official Action, the Examiner asserts that Claim 4 is indefinite for lack of sufficient antecedent basis for the recitation "said nucleic acid sequence" in lines 3 to 4 of the claim. Without conceding to the merits of this rejection, by the present amendment Applicants have amended claim 4 to recite "the nucleotide sequence of said nucleic acid of interest". Antecedent basis for this recitation can be found in claim 2 (see e.g. substep b) i.).

At page 3 of the Official Action, the Examiner asserts that Claim 8 is indefinite in its recitation of the limitation "the genome of the DNA". By the present Amendment, claim 8 has been amended to recite " the genome of said eucaryotic cell."

At page 3 of the Official Action, the Examiner argues that claims 40 and 41 are indefinite in their recitation of the limitation "the DNA region encoding said sense nucleotide sequence" and "the DNA region encoding said antisense nucleotide sequence" as these terms are purportedly lacking antecedent basis in claims 39 and claims 22 respectively. In the Examiner's view Claims 39 and 22 recite only "one DNA region which encodes both the sense and antisense sequences." Applicants submit that although indeed only one DNA region is recited encoding both the sense and antisense sequences, that DNA region consists of two parts, one part yielding upon transcription the region with the sense sequence and the other part encoding the region with the antisense sequence. By the present amendment, claims 40 and 41 have been amended in an effort to clarify this point.

In view of the foregoing, withdrawal of this rejection is respectfully requested.

Claims 1 to 12, 22, 25, 26 and 39-62 are rejected under 35 U.S.C. §112, first paragraph, as purportedly containing subject matter which is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art, that the inventors, at the time the application was filed, had possession of the claimed invention.

This rejection, to the extent that it applies to the claims as amended, is respectfully traversed.

At page 4 of the Official Action, the Examiner asserts that

> [c]laims 1-12, 22, 25, 26 and 39-62 are drawn to DNA vectors which produce an artificial hairpin RNA, wherein at least 75% of 10 consecutive bases of the sequence of the hairpin RNA hybridize to form the hairpin and wherein the sense and antisense sequences of the hairpin RNA are not naturally occurring simultaneously in one RNA.

The Examiner argues that Applicants "have not provided a written description for the genus of nucleotide sequences encompassed within the claims." More specifically, the Examiner asserts that "the specification has not described adequately what hairpin RNAs are not naturally occurring simultaneously in one RNA, nor has it provided the nucleotide sequence for target RNAs which have yet to be discovered."

Without conceding to the merits of this rejection, but solely in an effort to expedite prosecution, by the present Amendment the claims have been amended to remove the proviso that the "sense and antisense sequence are not naturally occurring simultaneously in one RNA molecule," as it has become redundant in view of the newly introduced claim term, as explained *supra*. The rejection, as it relates to the presence of this proviso in the claims, should therefore be rendered moot.

The presently claimed invention is broadly applicable for reduction of the expression of a wide range of target genes of interest. As discussed during the personal interview on September 5, 2002, the presently claimed methods for gene silencing can be analogized to methods for determining the nucleotide sequence of a gene or a DNA fragment, in that both are methods of general applicability, and are not dependent on the particular nucleotide sequences used by their respective inventors to demonstrate their claimed methods. It is inappropriate to limit the present claims to a particular exemplified target gene, just as it

would have been inappropriate to limit claims to methods for determining gene sequences to the particular genes sequenced.

At page 4 of the Official Action, the Examiner asserts that

> [a]dequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016.

However, the present case is easily distinguishable from *Fiers* and *Amgen,* both of which related to claims to particular nucleotide sequences. The present claims, by contrast, are directed to a generally applicable method for efficient gene silencing.

Moreover, the present specification provides examples for efficient reduction of the gene expression of such widely diverging genes as genes encoding β-glucuronidase, δ12-desaturase or PVY protease. Furthermore, disclosure of the presently claimed invention through scientific publications (published after the priority date of the present application) has led to a quick adaptation of this powerful method for gene silencing, and literature is replete with reports of the successful gene silencing using the currently claimed method for a wide variety of genes.

Thus, Applicants respectfully submit that persons skilled in the relevant art when reading this specification, would immediately recognize the broad applicability of the currently claimed invention on the basis of the exemplified reduction in gene expression of the widely divergent genes, in connection with the general description. In other words, the specification does reasonably convey to one skilled in the art that the inventors at the time the application was filed had possession of the claimed invention.

Whereas it is true that the current specification has not provided the nucleotide sequence for target RNAs which have yet to be discovered, Applicants respectfully submit

that this is immaterial. Indeed, once a new target gene has been isolated, one of ordinary skill in the art would be able, without undue experimentation, to determine its sequence, and based on that information design the chimeric DNAs according to the presently claimed invention. In fact, it is not even necessary for one practicing the presently claimed invention to know the nucleotide sequence of the target gene of interest, as indicated in the present specification.

> In its most straightforward embodiment, the RNA molecule comprising both the sense and antisense nucleotide sequences to at least part of a nucleic acid of interest, suitable for the methods of the invention, can be obtained by cloning two copies of a DNA region with the selected target sequence in inverted repeat orientation (preferably separated by a short DNA region which does not contain a transcription termination signal, and encodes the spacer sequence) under a suitable promoter. This chimeric DNA is then either used as template DNA in an in vitro transcription method to generate the RNA molecule, which is introduced in the host cell, or the chimeric DNA itself is introduced in the host cell.

(*see* page 27, second paragraph). Thus, according to the teaching of this embodiment of the claimed invention, it is not even required to have the nucleotide sequence for target genes of interest.

In view of the above, withdrawal of the rejection is respectfully requested.

CONCLUSION

From the foregoing, favorable action in the form of a Notice of Allowance is believed to be next in order, such action is earnestly solicited.

In the event that there are any questions concerning this Amendment, or the Application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of the Application may be expedited.

Respectfully submitted,

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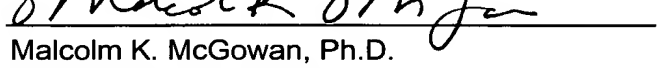
By: 
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Date: January 16, 2003

Attachment to Reply and Amendment dated January 16, 2003

Marked-up Claims 1, 2, 4, 8, 22, 40, 42, 50, 56, 58

1.[Four times Amended] A method for reducing the phenotypic expression of a nucleic acid of interest, which is normally capable of being expressed in a eucaryotic cell, comprising the step of introducing a chimeric DNA comprising the following operably linked parts:

a) a promoter, operative in said eucaryotic cell;

b) a DNA region, which when transcribed, yields an RNA molecule comprising an RNA region capable of forming an artificial hairpin RNA structure comprising two annealing RNA sequences, wherein one of the annealing RNA sequences of the hairpin RNA structure comprises a sense sequence, essentially similar to at least 10 consecutive nucleotides of the nucleotide sequence of said nucleic acid of interest, and wherein the second of said annealing RNA sequences comprises an antisense sequence essentially similar to at least 10 consecutive nucleotides of the complement of at least part of said nucleotide sequence of said nucleic acid of interest[, provided that said sense and said antisense sequence are not naturally occurring simultaneously in one RNA molecule]; and [optionally]

c) a DNA region involved in transcription termination and polyadenylation[.];

wherein said DNA region, which when transcribed yields said RNA molecule, comprises a heterologous intron sequence.

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Marked-up Claims 1, 2, 4, 8, 22, 40, 42, 50, 56, 58

2. [Amended] A method for reducing the phenotypic expression of a nucleic acid of interest, which is normally capable of being expressed in a eucaryotic cell, comprising the step of introducing a chimeric DNA comprising the following operably linked parts:

a.) a promoter, operative in said eucaryotic cell;

b.) a DNA region, which when transcribed, yields an RNA molecule with a nucleotide sequence comprising

i.) a sense nucleotide sequence including at least 10 consecutive nucleotides having between about 75 and about 100% sequence identity with at least 10 consecutive nucleotides of the nucleotide sequence of said nucleic acid of interest; and

ii.) an antisense nucleotide sequence including at least 10 consecutive nucleotides, having about 75% to about 100% sequence identity with the complement of said at least 10 consecutive nucleotides of said sense nucleotide sequence;

wherein the RNA is capable of forming an artificial hairpin RNA structure with a double stranded RNA stem by base-pairing between the regions with sense and antisense nucleotide sequence such that said at least 10 consecutive nucleotides of the sense sequence basepair with said at least 10 consecutive nucleotides of the antisense sequence[, provided that said sense sequence and said antisense sequence are not naturally occurring simultaneously in one RNA molecule]; and [optionally]

c.) a DNA region involved in transcription termination and polyadenylation[.];

wherein said DNA region, which when transcribed yields said RNA molecule, comprises a heterologous intron sequence.

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Marked-up Claims 1, 2, 4, 8, 22, 40, 42, 50, 56, 58

4. [Twice Amended] The method of claim 2, wherein said sense nucleotide sequence comprises at least about 550 consecutive nucleotides having between 75% and 100% sequence identity with at least about 550 consecutive nucleotides of the nucleotide sequence of said nucleic acid of interest.

8. [Amended] The method of claim 2, wherein said chimeric DNA is stably integrated in the genome of [the DNA] said eucaryotic cell.

22. [Twice Amended] A eucaryotic cell, comprising a nucleic acid of interest, which is normally capable of being phenotypically expressed, further comprising a chimeric DNA molecule comprising the following operably linked parts:

a) a promoter, operative in said eucaryotic cell;

b) a DNA region, which when transcribed, yields an RNA molecule with at least one RNA region with a nucleotide sequence comprising

i. a sense nucleotide sequence including at least 10 consecutive nucleotides having between 75 and 100% sequence identity with at least 10 consecutive nucleotides of the nucleotide sequence of the nucleic acid of interest; and

ii. an antisense nucleotide sequence including at least 10 consecutive nucleotides, having between about 75% to about 100% sequence identity with the complement of said at least 10 consecutive nucleotides of said sense nucleotide sequence;

wherein the RNA is capable of forming an artificial hairpin RNA structure with a double stranded RNA stem by base-pairing between the regions with sense and

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Marked-up Claims 1, 2, 4, 8, 22, 40, 42, 50, 56, 58

antisense nucleotide sequence, [provided that said sense sequence and said antisense sequence are not naturally occurring simultaneously in one RNA molecule]; and [optionally]

c) a DNA region involved in transcription termination and polyadenylation[.] ; wherein said DNA region, which when transcribed yields said RNA molecule, comprises a heterologous intron.

40. [Amended] The method of claim [39] 2, wherein said intron is located between [the] part of said DNA region [encoding] which when transcribed yields said sense nucleotide sequence and [the] part of said DNA region [encoding] which when transcribed yields said antisense nucleotide sequence.

42. [Amended] The eucaryotic cell of claim [41] 22, wherein said intron is located between [the] part of said DNA region [encoding] which when transcribed yields said sense nucleotide sequence and [the] part of said DNA region which when transcribed yields encoding said antisense nucleotide sequence.

50. [Amended] The method of claim [49] 44, wherein said intron is located between [the] part of said DNA region [encoding] which when transcribed yields said sense nucleotide sequence and [the] part of said DNA region [encoding] which when transcribed yields said antisense nucleotide sequence.

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Marked-up Claims 1, 2, 4, 8, 22, 40, 42, 50, 56, 58

56. [Amended] The eucaryotic cell of claim [55] 53, wherein said intron is located between [the] part of said DNA region [encoding] which when transcribed yields said sense nucleotide sequence and [the] part of said DNA region [encoding] which when transcribed yields said antisense nucleotide sequence.

58. [Amended] The eucaryotic cell of claim [57] 54, wherein said intron is located between [the] part of said DNA region [encoding] which when transcribed yields said sense nucleotide sequence and [the] part of said DNA region [encoding] which when transcribed yields said antisense nucleotide sequence.